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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

006808

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

7/26/1988

**MEMORANDUM**

**SUBJECT:** Supplemental submission for subchronic neurotoxicity study (90 day chickens); Record no. 223900; EPA ID no. 3125-326; MRID No. 404597-01; Proj. No. 8-089; Caswell No. 447AB

**TO:** John T. Tice (PM 16)  
Registration Division (TS-767C)

**FROM:** James N. Rowe, D.  
Section V, Toxicology Branch  
Hazard Evaluation Branch (TS-769C)

*James N. Rowe*  
7/26/88

**THRU:** Quang Q. Bui, Ph.D. *Quang Bui* 7/26/88  
Section Head  
Section V, Toxicology Branch  
Hazard Evaluation Division (TS-769C)

Theodore M. Farber, Ph.D.  
Chief, Toxicology Branch  
Hazard Evaluation Division (TS-769C)

**ACTION:** Review supplemental submission for subchronic neurotoxicity study (90 day chickens); Record no. 223900; EPA ID no. 3125-326; MRID No. 404597-01; Proj. No. 8-0897; Caswell No. 447AB

**RECOMMENDATIONS:**

The additional submitted data presented along with the rationale presented by the registrant are adequate to allow the conclusion that the subchronic administration of Isofenphos® did not produce any appreciable neuropathological effects in the chickens. However, the registrant is encouraged to utilize younger animals in future neurotoxicity studies of this nature.

This study is upgraded to Core Minimum data.

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DATA EVALUATION RECORD

Issue: Response to EPA request for more information regarding axonal degeneration in control chickens used in subchronic neurotoxicity study.

## REGISTRANT COMMENT:

"With regard to the high incidence of slight axonal degeneration that was seen in the 90-day neurotoxicity study of ISOFENPHOS (Mobay report no. 90231), it is our belief that the incidence of this lesion did not interfere with the interpretation of this study. Nor did we believe that it masked a neurotoxic effect. The reasoning behind our conclusions is as follows:

1. The incidence and severity of axonal degeneration that occurred in the control group was also identical to that seen in the high dose group hens (see Table II). If ISOFENPHOS was neurotoxic one would expect, at the least, that the severity of these lesions would have been greater in the high dose group than in the control group birds. It is evident from Table II that this was not the case.
2. With a background incidence of a lesion that varies as greatly as does axonal degeneration in chickens, coupled to the relatively high background occurrence of this lesion, it is of critical importance to have appropriate concurrent controls for these types of studies. In fact, in this situation, concurrent controls are probably of greater importance than historical control data. In this study, we believe appropriate concurrent controls were used.
3. In the case of organophosphate-induced neuropathy, one would expect the incidence and/or severity of axonal degeneration/demyelination of the spinal cord to be greater in the lumbo-sacral region than the cervical region. This was certainly the case for the tri-ortho-cresylophosphate (TOCP) positive control group in the 90-day neurotoxicity study of ISOFENPHOS (see Table II). On the other hand, the high dose group treated with ISOFENPHOS showed no increase in severity of axonal degeneration in any of the three spinal regions over the control group. Furthermore, from Table 1 it is obvious that the incidence of lumbo-sacral axonal degeneration in the 90-day neurotoxicity study of ISOFENPHOS remained within historical bounds when compared to younger control hens of other studies.
4. The incidence and severity of axonal degeneration that occurred in the positive control group exposed to TOCP was increased relative to the control or ISOFENPHOS-treated birds. This indicates that, despite the high background incidence of this lesion, an organophosphate-induced neuropathy would have been observable. Thus, the fact that

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the incidence and severity of these lesions remained unchanged in the ISOFENPHOS-treated chickens relative to the controls, supports the contention that ISOFENPHOS was not neurotoxic in this study."

EPA RESPONSE:

The reviewer is in general agreement with registrant's comments, including the fact that the axonal degeneration observed in the control animals is a normal background change. The degree of slight axonal degeneration in the controls appears to be within or approach the historical control values for White leghorn hens for cervical and lumbo-sacral axonal degeneration. Thoracic axonal degeneration lies well outside the historical control range but the reviewer would attribute this to the older age range of hens found in the study group under discussion as compared to other study groups.

The age range of hens stated in the present submission is considerably older than that recommended by the EPA guidelines (8-14 months) and the age range is not identical to that originally stated by the registrant (15-20 months, Methods Section 3.2, Laboratory animals and husbandry), an apparent oversight upon the part of the testing facility. The reviewer still considers the normal background incidence of axonal degeneration observed in the control hens to be higher than optimal, nevertheless, the additional submitted data along with the rationale presented by the registrant are adequate to allow the conclusion that the subchronic administration of Isofenphos did not produce any appreciable neuropathological effects in the chickens. However, the registrant is encouraged to utilize younger animals in future neurotoxicity studies of this nature.

This study is upgraded to Core Minimum data.

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